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Authors

Beveridge, Louise

Struthers, Allan

Khan, Faisel

et al.

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Effect of Vitamin D Supplementation on Blood Pressure:

A Systematic Review and Meta-analysis Incorporating Individual Patient Data

Louise A. Beveridge, MB, ChB,
Medical Research Institute, University of Dundee, Ninewells Hospital, Dundee, Scotland

Allan D. Struthers, MD,
Medical Research Institute, University of Dundee, Ninewells Hospital, Dundee, Scotland

Faisel Khan, PhD,
Medical Research Institute, University of Dundee, Ninewells Hospital, Dundee, Scotland

Rolf Jorde, PhD,
Tromsø Endocrine Research Group, Institute of Clinical Medicine, UiT (Universitetet i Tromsø), The Arctic University of Norway, Tromsø, Norway

Robert Scragg, MBBS, PhD,
School of Population Health, University of Auckland, Auckland, New Zealand

Helen M. Macdonald, PhD,
School of Medicine and Dentistry, University of Aberdeen, Aberdeen, Scotland

Jessica A. Alvarez, PhD, RD,
Division of Endocrinology, Metabolism and Lipids, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia

Rebecca S. Boxer, MD, MS,
Division of Geriatric Medicine, University of Colorado School of Medicine, Aurora

Andrea Dalbeni, MD,
Department of Medicine, University of Verona, Verona, Italy

Corresponding Author: Miles D. Witham, BM, BCh, PhD, Medical Research Institute, University of Dundee, Ninewells Hospital, Dundee DD1 9SY, Scotland, (m.witham@dundee.ac.uk).

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Critical revision of the manuscript for important intellectual content: All authors.
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Group Information: The D-PRESSURE Collaboration consists of the named authors: Louise A. Beveridge, MB, ChB; Allan D. Struthers, MD; Faisel Khan, PhD; Rolf Jorde, PhD; Robert Scragg, MBBS, PhD; Helen M. Macdonald, PhD; Jessica A. Alvarez, PhD, RD; Rebecca S. Boxer, MD, MS; Andrea Dalbeni, MD; Adam D. Gepner, MD; Nicole M. Isbel, MBBS, PhD; Thomas Larsen, MD, PhD; Jitender Nagpal, MBBS, MD; William G. Petchey, BM, PhD; Hans Stricker, MD; Franziska Strobel, MD; Vin Tangpricha, MD, PhD; Laura Toxqui, PhD; M. Pilar Vaquero, PhD; Louise Wamberg, MD, PhD; Armin Zittermann, PhD; and Miles D. Witham, BM, BCh, PhD.

Adam D. Gepner, MD,
Division of Cardiovascular Medicine, University of Wisconsin School of Medicine and Public Health, Madison

Nicole M. Isbel, MBBS, PhD,
Department of Nephrology, Princess Alexandra Hospital, Brisbane, Australia

Thomas Larsen, MD, PhD,
Department of Medical Research, Holstebro Hospital, Holstebro, Denmark

Jitender Nagpal, MBBS, MD,
Department of Pediatrics and Clinical Epidemiology, Sitaram Bhartia Institute of Science and Research, New Delhi, India

William G. Petchey, BM, PhD,
Department of Nephrology, Cambridge University Hospitals NHS (National Health Service) Foundation Trust, Cambridge, England

Hans Stricker, MD,
Angiology Unit, Ospedale La Carità, Locarno, Switzerland

Franziska Strobel, MD,
Department of Internal Medicine, Asklepios-Paulinenklinik, Wiesbaden, Germany

Vin Tangpricha, MD, PhD,
Division of Endocrinology, Metabolism and Lipids, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia

Laura Toxqui, PhD,
Department of Metabolism and Nutrition, Institute of Food Science, Technology, and Nutrition, Spanish National Research Council, Madrid, Spain

M. Pilar Vaquero, PhD,
Department of Metabolism and Nutrition, Institute of Food Science, Technology, and Nutrition, Spanish National Research Council, Madrid, Spain

Louise Wamberg, MD, PhD,
Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

Armin Zittermann, PhD,
Heart and Diabetes Center North Rhine–Westphalia, Ruhr University Bochum, Bochum, Germany

Miles D. Witham, BM, BCh, PhD, and
Medical Research Institute, University of Dundee, Ninewells Hospital, Dundee, Scotland

for the D-PRESSURE Collaboration

Abstract

IMPORTANCE—Low levels of vitamin D are associated with elevated blood pressure (BP) and future cardiovascular events. Whether vitamin D supplementation reduces BP and which patient characteristics predict a response remain unclear.

OBJECTIVE—To systematically review whether supplementation with vitamin D or its analogues reduce BP.

DATA SOURCES—We searched MEDLINE, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials, and http://www.ClinicalTrials.com augmented by a hand search of references from the included articles and previous reviews. Google was searched for gray literature (ie, material not published in recognized scientific journals). No language restrictions were applied. The search period spanned January 1, 1966, through March 31, 2014.

STUDY SELECTION—We included randomized placebo-controlled clinical trials that used vitamin D supplementation for a minimum of 4 weeks for any indication and reported BP data. Studies were included if they used active or inactive forms of vitamin D or vitamin D analogues. Cointerventions were permitted if identical in all treatment arms.

DATA EXTRACTION AND SYNTHESIS—We extracted data on baseline demographics, 25-hydroxyvitamin D levels, systolic and diastolic BP (SBP and DBP), and change in BP from baseline to the final follow-up. Individual patient data on age, sex, medication use, diabetes mellitus, baseline and follow-up BP, and 25-hydroxyvitamin D levels were requested from the authors of the included studies. For trial-level data, between-group differences in BP change were combined in a random-effects model. For individual patient data, between-group differences in BP at the final follow up, adjusted for baseline BP, were calculated before combining in a random-effects model.

MAIN OUTCOMES AND MEASURES—Difference in SBP and DBP measured in an office setting.

RESULTS—We included 46 trials (4541 participants) in the trial-level meta-analysis. Individual patient data were obtained for 27 trials (3092 participants). At the trial level, no effect of vitamin D supplementation was seen on SBP (effect size, 0.0 [95% CI, −0.8 to 0.8] mm Hg; $P = .97$; $I^2 = 21\%$) or DBP (effect size, −0.1 [95% CI, −0.6 to 0.5] mm Hg; $P = .84$; $I^2 = 20\%$). Similar results were found analyzing individual patient data for SBP (effect size, −0.5 [95% CI, −1.3 to 0.4] mm Hg; $P = .27$; $I^2 = 0\%$) and DBP (effect size, 0.2 [95% CI, −0.3 to 0.7] mm Hg; $P = .38$; $I^2 = 0\%$). Subgroup analysis did not reveal any baseline factor predictive of a better response to therapy.

CONCLUSIONS AND RELEVANCE—Vitamin D supplementation is ineffective as an agent for lowering BP and thus should not be used as an antihypertensive agent.

A wealth of observational data has demonstrated relationships between circulating vitamin D metabolite levels and blood pressure (BP). Lower 25-hydroxyvitamin D (25OHD) levels are associated with higher BP levels in cross-sectional studies[1,2] and with increased rates of incident hypertension.[3] Such observations are underpinned by a number of biologically plausible mechanisms and the fact that vitamin D receptors are found on endothelial cells, smooth muscle cells, and myocytes.[4] Vitamin D has been shown to improve endothelial function in some studies,[5,6] reduce the production of proinflammatory cytokines,[7] reduce activity of the renin-angiotension-aldosterone system, and reduce parathyroid hormone

(PTH) levels.[8] Parathyroid hormone has been posited as vasculotoxic in its own right. Any or all of these mechanisms therefore potentially mediate an effect of vitamin D on BP levels.

Intervention studies to date have produced conflicting evidence on the BP-lowering effect of vitamin D. One previous meta-analysis[9] based on a number of small trials demonstrated a modest but significant decrease in BP in studies in which the mean BP reading was elevated at baseline; another meta-analysis[10] conducted at a similar time did not demonstrate a significant effect of vitamin D supplementation on BP; and a more recent meta-analysis[11] showed a small decrease in diastolic BP (DBP) but not systolic BP (SBP). Although the effects of vitamin D on BP appeared to be small in previous meta-analyses, even a modest improvement in BP would be of public health importance because widespread supplementation with vitamin D would be an inexpensive intervention. Furthermore, selected subgroups (eg, nonwhite populations and those with very low 25OHD levels) could benefit to a greater extent, potentially making vitamin D part of the therapeutic armamentarium in treating individuals with hypertension.

In the 5 years since the first meta-analyses were published, a proliferation of randomized clinical trials has studied vitamin D and cardiovascular health. We therefore sought to update a systematic review of randomized clinical trials[9] to evaluate whether vitamin D supplementation reduces BP when compared with placebo across a range of study populations and vitamin D analogues. We also sought to perform an individual patient data meta-analysis to explore further which subgroups of patients might derive the greatest benefit.

Methods

Review Design

We conducted a systematic review based on a predefined protocol. The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002816). Institutional review board approval was not required, and data were deidentified at the source before transfer. We included randomized clinical trials that reported BP or other measures of vascular function, including arterial stiffness, endothelial function, and left ventricular mass index, as outcomes. We searched MEDLINE, CINAHL, EMBASE, the Cochrane Central Register of Controlled Trials, and http://www.ClinicalTrials.com using our strategy. We also searched for gray literature (ie, material not published in recognized scientific journals) using Google and hand searched the references of included articles and previous reviews of vitamin D therapy. No language restrictions were applied to eligible reports. The search period spanned January 1, 1966, through March 31, 2014. Two of us (L.A.B. and M.D.W.) conducted the search.

Search Strategy

Search terms included *vitamin D*, *vitamin D_3*, *vitamin D_2*, *cholecalciferol*, *ergocalciferol*, *alphacalcidol*, *alfacalcidol*, *paricalcitol*, and *doxercalciferol* combined with *blood pressure*, *hypertension*, *cardiovascular*, *mortality*, *randomized controlled trials*, or *placebo*. The

electronic search strategy used for MEDLINE is described in the eAppendix in the Supplement.

Study Selection

We considered studies with participants with any reported baseline 25OHD level. Studies with BP reduction or changes in surrogate markers of cardiovascular risk were included; a minimum of 4 weeks of therapy was necessary for inclusion in the review to ensure that the intervention had sufficient time to produce an effect. We included the following interventions: vitamin D_2 (ergocalciferol), vitamin D_3 (cholecalciferol), calcitriol (1,25-hydroxyvitamin D_3), 1-α-hydroxylated versions of vitamin D, paricalcitol, and doxerocalciferol. Control groups receiving placebo were used, and those receiving placebo plus a cointervention were included if both arms of the study received the cointervention. Studies from primary and secondary care or population settings were included. We placed no restrictions on sex or ethnicity. We did not include any studies recruiting participants younger than 16 years or studying patients who were receiving dialysis. The primary outcome of the meta-analysis was the change in office-measured SBP and DBP readings from baseline through follow-up.

Data Extraction

Two researchers (L.A.B. and M.D.W.) independently extracted data from all trial reports with data collection forms used in a previous systematic review.[9] Differences were resolved by consensus. The following data were recorded for all eligible studies: sex, age, smoking status, social class, ethnic group/skin color, functional status/dwelling place, diabetes mellitus status and glycated hemoglobin level, kidney function, history of cardiovascular events, history of hypertension, baseline BP reading, and baseline use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, statins, and aspirin. For use in this analysis, we recorded change in office-measured SBP and DBP readings and change in 24-hour BP as outcome measures. We contacted the study authors to provide missing data or to clarify data that were unclear from primary reports.

IPD Collection

For all eligible studies, the authors were approached to provide individual patient data to conduct subgroup analyses by baseline characteristics at the patient level, in particular by baseline 25OHD level, baseline medication use, baseline BP level, and the presence of diabetes mellitus. The following data were requested for each patient: age; sex; body mass index; ethnicity; month of recruitment; SBP and DBP readings at baseline and follow-up; vitamin D supplement given (type, dose, frequency, and duration); baseline 25OHD level (and follow-up 25OHD level if available); baseline and posttreatment levels of PTH, serum calcium/albumin, total cholesterol, and high-density lipoprotein cholesterol levels; diagnosis of diabetes mellitus, previous stroke, or myocardial infarction at baseline; and whether patients were receiving an ACE inhibitor, statin, or angiotensin receptor antagonist at baseline.

Risk for Bias Assessment

We assessed each included study for risk for bias using fields from the Delphi checklist[12] to assess the following variables: quality of random allocation concealment, intention-to-treat analysis, blinding of outcome assessors, treatment and control group comparability, clear definition of inclusion and exclusion criteria, participant blinding to allocation, and description of withdrawals and dropouts. We generated funnel plots to examine possible publication bias; these were supplemented by formal statistical testing using the Egger test.[13] Study quality was assessed independently by 2 of us (L.A.B. and M.D.W.), and discrepancies were resolved by consensus.

Strategy for Data Synthesis

We performed the meta-analysis at the trial level using commercially available software (Comprehensive Meta-analysis; Biostat). We used the weighted squares method with random-effects models in all cases. For all treatment effects, a negative value denotes a reduction in BP with the intervention compared with placebo. For each analysis at the trial level, the mean change from baseline to the last follow-up reported was compared between groups because these data were most commonly supplied in trial-level reports. For studies with more than 1 vitamin D group, the highest dose of vitamin D or an analogue was compared with the control group; intermediate dose groups did not undergo analysis. Heterogeneity was assessed using the I^2 test. Preplanned subgroup analyses were performed to examine the effects of different preparations of vitamin D, dose ranges, and baseline BP. Degree of change in BP was regressed against baseline BP, trial duration, daily dose equivalent of vitamin D given, and mean baseline 25OHD level.

For the individual patient data analysis, a 2-stage analysis was performed, as recommended by Riley et al.[14] For each study, the mean BP values for each group at the final follow-up were calculated and adjusted for baseline values using analysis of covariance (SPSS, version 21; IBM). These values were then combined using weighted least-squares random-effects models with commercially available software (Rev-Man 5.3; Cochrane Collaboration). For studies with more than 1 vitamin D dose, patients taking the highest dose were compared with those taking a placebo; patients taking the lower dose were excluded from the analysis. We performed the following prespecified patient-level subgroup analyses using these methods: diabetes mellitus vs no diabetes mellitus; ACE inhibitor vs no ACE inhibitor; baseline SBP of no greater than 140 mm Hg vs greater than 140 mm Hg; DBP of no greater than 90 mm Hg vs greater than 90 mm Hg; baseline PTH level of no greater than vs greater than the median level for the individual patient data set; and baseline 25OHD level of less than 10, 10 to 20, and greater than 20 ng/mL (to convert to nanomoles per liter, multiply by 2.496). For analyses of ACE inhibitor use, patients taking angiotensin receptor blockers were excluded given the similar but not identical biological effect of these agents. Exploratory post hoc analyses were undertaken for subgroups with combinations of risk factors (high BP, low 25OHD levels, and higher PTH levels), nonwhite participants, and summer vs winter enrollment. The northern hemisphere summer was defined as June through August and winter as December through February, with the definitions inverted for southern hemisphere studies.

Results

Details of the search process are given in Figure 1. We included 52 studies in the systematic review[5,7,15–63]; 46 of these studies* yielded data that could be combined in the trial-level meta-analysis. Six studies used mean arterial pressure or reported median BP readings, and we were unable to obtain mean readings from the authors. We successfully obtained 27 data sets for the individual patient data analysis. For the trials from which we did not succeed in obtaining individual patient data, 2 author groups felt unable to share their data, 1 author group agreed but did not supply data, and in all other cases, authors did not respond to requests or could not be contacted. Details of all included studies are given in eTable 1 in the Supplement. Six trials[15–19,33] used 1-α-hydroxylated vitamin D derivatives or calcitriol; 4 trials,[23,29,49,62] paricalcitol; and the other trials, ergocalciferol or cholecalciferol.

Quality Assessment and Publication Bias

Results of the quality assessments performed by assessing the risk for bias across a range of domains are shown in eTable 2 in the Supplement. Allocation concealment was deemed adequate in 51 of 52 trials,[5,7,15–32,34–63] and most trials had adequate blinding for participants (49 of 52),[5,7,16–32,34–45,47–63] other health care staff (49 of 52),[5,7,16–32,34–45,47–63] and outcomes assessment (46 of 52).† Only 22 of 52 trials‡ clearly described analysis on intention to treat. Of the 30 trials in which intention to treat was not well described, 19 trials did not perform analyses on an intention-to-treat basis. Visual inspection of the funnel plot for SBP treatment effect (eFigure 1 in the Supplement) revealed no obvious asymmetry to suggest publication bias; results of the Egger test were not significant ($P = .62$).

Main Outcome Measures for Trial-Level Data

Meta-analysis of the change in BP between baseline and the final follow-up for each trial revealed no clinically or statistically significant effect on SBP (treatment effect, 0.0 [95% CI, −0.8 to 0.8] mm Hg; $P = .97$; $I^2 = 21\%$) or DBP (treatment effect, −0.1 [95% CI, −0.6 to 0.5] mm Hg; $P = .84$; $I^2 = 20\%$). Forest plots for the overall effect of treatment on SBP and DBP are presented in Figure 2 and eFigure 2 in the Supplement, respectively. Prespecified subgroup analyses are shown in Table 1; analysis by baseline BP category, type of intervention, dose interval, or baseline 25OHD category did not affect the results significantly.

Trial-Level Meta-regression

No significant relationship was found at the trial level between SBP treatment effect and mean baseline SBP (slope, 0.016 [95% CI, −0.037 to 0.069] mm Hg per 1–mm Hg increase of baseline SBP measurement; $P = .55$) (eFigure 3 in the Supplement), baseline 25OHD level (slope, 0.003 [95% CI, −0.014 to 0.021] mm Hg per 1-ng/mL increase of baseline 25OHD level; $P = .70$), baseline PTH level (slope, −0.009 [95% CI −0.036 to 0.053] mm Hg

*References 5, 15–18, 21, 22, 24–36, 39–63
†References 5, 7, 17, 19–32, 34–43, 45, 47–63
‡References 16, 18, 21–24, 28, 29, 32, 34, 41, 43, 45, 48, 51, 53, 55–57, 59, 62, 63

per 1-pg/mL increase of baseline PTH level; $P = .53$) (to convert to micromoles per liter, divide by 9.43), or trial duration (slope, 0.007 [95% CI, −0.005 to 0.019] mm Hg per month of the trial; $P = .27$). Similarly, for trials using vitamin D_3, no significant relationship was found on meta-regression between SBP treatment effect and the daily dose equivalent used as treatment (slope, −0.001 [95% CI, −0.018 to 0.018] mm Hg per 1-U dose of vitamin D_3; $P = .93$). Small numbers of trials precluded meta-regression of the daily dose effects of vitamin D_2, paricalcitol, or 1-α-hydroxylated vitamin D derivatives. Meta-regression of the DBP treatment effect against baseline variables similarly showed no significant relationships for mean baseline DBP (slope, 0.001 [95% CI, −0.003 to 0.006] mm Hg per 1–mm Hg increase in baseline DBP; $P = .54$), baseline 25OHD level (slope, −0.001 [95% CI, −0.005 to 0.003] mm Hg per 1-ng/mL increase of baseline 25OHD level; $P = .67$), baseline PTH level (slope, −0.020 [95% CI, −0.051 to 0.011] mm Hg per 1-pg/mL increase of baseline PTH level; $P = .21$), trial duration (slope, 0.007 [95% CI, −0.005 to 0.020] mm Hg per month of trial; $P = .23$), and daily dose equivalent (slope, 0.000 [95% CI, 0.000 to 0.001] mm Hg per 1-U dose of vitamin D_3; $P = .34$).

Individual Patient Data Analyses

Analyses of the individual patient data sets for SBP and DBP are shown in Figure 3 and eFigure 4 in the Supplement, respectively, with subgroup analyses shown in Table 2. The overall treatment effect derived from the individual patient data sets was similar to that derived from the trial-level data, despite the use of a smaller number of trials, for SBP (treatment effect, −0.4 [95% CI, −1.2 to 0.4] mm Hg; $P = .27$; $I^2 = 0\%$) and DBP (treatment effect, −0.2 [95% CI, −0.7 to 0.3] mm Hg; $P = .38$; $I^2 = 0\%$). In subgroup analyses, no significant differences were seen between patients with or without diabetes mellitus, between those taking or not taking ACE inhibitors or by subgroups of baseline BP, PTH level, or 25OHD level (Table 2).

Analysis of the small group of patients with a combination of baseline factors potentially most likely to benefit (SBP >140 mm Hg; 25OHD level <10 ng/mL; and PTH level >217 pg/mL) showed no evidence of benefit (60 patients; treatment effect on SBP, 2.7 [95% CI, −5.0 to 10.4] mm Hg, $P = .49$; $I^2 = 0\%$). Similarly, analysis of participants of nonwhite ethnicity (n = 214) showed no evidence of benefit for SBP (treatment effect, 2.2 [95% CI, −1.1 to 5.4] mm Hg; $P = .19$; $I^2 = 28\%$) and DBP (treatment effect, 0.4 [95% CI, −1.7 to 2.6] mm Hg; $P = .70$; $I^2 = 11\%$). Comparison of patients recruited during the summer and winter months did not reveal any significant differences between the SBP treatment effect for the summer (−1.1 [95% CI, −4.1 to 2.0] mm Hg; $P = .50$; $I^2 = 37$) or for the winter (1.3 [95% CI, −1.4 to 4.0] mm Hg; $P = .35$, $I^2 = 60\%$) or between the DBP treatment effect for the summer (1.4 [95% CI, −0.4 to 3.2] mm Hg; $P = .11$; $I^2 = 38\%$) or for the winter (0.8 [95% CI, −0.1 to 1.6] mm Hg; $P = .07$; $I^2 = 0\%$).

Discussion

Our analysis found no evidence of BP reduction by supplementation with vitamin D or vitamin D analogues, a result that was consistent between the trial-level and individual patient data analyses. Subgroup analyses found no evidence of BP reduction in patients with

elevated baseline BP or in patients with diabetes mellitus; in addition, we found no relationship between the effect of supplementation on BP and the use of ACE inhibitors, baseline 25OHD level, baseline BP, or baseline PTH level. The narrow CIs around the main result suggest that a clinically significant reduction in BP is unlikely based on the doses of vitamin D studied in this analysis; the lack of effect argues against a role for vitamin D supplementation as a means of BP control in individual patients or as a population-based intervention to reduce BP. These results are broadly consistent with those of previous meta-analyses,[9–11] although they contrast with the small reduction in BP in trials with high baseline BP found in a previous meta-analysis.[9] However, our analysis includes a much larger number of studies than previous analyses and therefore a larger number of patients and a larger range of doses. Our use of individual patient data allowed us to examine whether particular subgroups might still benefit from vitamin D supplementation, which previous analyses have not been able to address.

Although the number of included patients is greater than in previous meta-analyses and the use of individual patient data has allowed analysis of subgroups, limitations to this systematic review remain. The included studies are almost all single-center trials, and most are of modest size; none recruited more than 1000 patients. As a result, baseline imbalances between trials were common, and such imbalances are difficult to correct for fully, even with individual patient data analysis.[14] Not all studies were of high quality; we noted deficiencies in intention to treat and in reporting of masking and allocation concealment. All eligible studies may not have been included, although our wide search strategy, contact with leading authors in the field, lack of a language restriction, and search of the gray literature minimized this issue. Nevertheless, other BP data may exist (eg, from osteoporosis trials) that have not been published yet and that we have been unable to locate.[64] An additional limitation is the small number of trials that have specifically targeted patients with hypertension at baseline; such patients perhaps would be more likely to respond to antihypertensive interventions. We did not see an effect of vitamin D supplementation even in this subgroup, although the high level of background treatment with antihypertensives and other cardiovascular medications known to interact with vitamin D (eg, statins) may again obscure detection of small treatment effects.

Debate continues as to what level of 25OHD constitutes a biological optimum and what level of vitamin D supplementation is necessary to achieve that optimum. Levels of more than 30 ng/mL have been postulated as necessary for optimum health,[65] but such levels are based on observational data and do not indicate the level required for maximal antihypertensive effects. Levels of vitamin D supplementation required to reach such levels vary widely depending on age, sex, obesity, and baseline 25OHD levels; doses ranging from 1600 to more than 5000 IU/d have been advocated as necessary.[66,67] Most doses studied in this review were at or below the lower end of this range, and several studies used intermittent dosing (weekly, monthly, or less frequent). Intermittent doses may have different biological effects[68] when compared with smaller regular doses; intermittent doses appeared to be less effective at reducing the incidence of respiratory tract infection in a recent systematic review,[69] although no such effect was evident for BP reduction in our analysis. Although larger, more frequent doses of vitamin D might still have effects on reducing BP, we found no evidence of a dose-response relationship in our analyses. Furthermore, most

studies included participants of European ancestry, and beneficial effects cannot be excluded in other ethnic groups, although our subgroup analysis did not find evidence to support such exclusion.

The results of this analysis add to the growing body of literature casting doubt on the ability of vitamin D supplementation to influence health outcomes beyond falls, fractures, and possibly respiratory tract infection and all-cause mortality.[69,70] Recent analyses have shown that although observational data suggest an association between low 25OHD levels and cardiovascular events, diabetes mellitus, and many cancers, intervention data do not support an effect across most of these diseases.[71] This lack of effect may exist in part because of the difficulty in fully disentangling low 25OHD levels from other closely associated factors (eg, aging, obesity, smoking, inactivity) that affect 25OHD levels and promote disease, but also in part because not all studies have targeted patients with the lowest circulating 25OHD levels. Another possibility is that 25OHD is a consequence, rather than a cause, of disease or disease precursor states; inflammatory responses have been shown to acutely reduce 25OHD levels,[72] although whether chronic inflammation caused by subclinical disease can have the same effect is not known. Vitamin D may have beneficial actions on cardiovascular health that are not captured by office brachial artery BP measurement, which has been argued to be less reliable than other measures, such as ambulatory BP measurement or central aortic BP measurement, although previous work suggests that the central effects of antihypertensives may be smaller than effects on peripherally measured BP.[73] Alternative mechanisms of action of vitamin D, such as alteration of endothelial function or markers of thrombogenicity, have been postulated,[5,56] and trials examining vascular events as the primary outcome are still required to examine these possibilities. Such trials of vitamin D supplementation are now under way in Finland, New Zealand, and the United States, and the results of these trials should further clarify the position of vitamin D in the cardiovascular therapeutic armamentarium. Recent data from a large mendelian randomization study[74] suggest that alleles linked to higher circulating 25OHD levels are associated with slightly lower SBP and DBP and a lower risk for hypertension. These findings are not inconsistent with our results, however; mendelian randomization studies are predicated on the alleles in question having no effects on the vascular system other than their effect on 25OHD levels, which may not be the case for the alleles tested (cytochrome *CYP21R* and *DHCR7*, a cholesterol-metabolizing gene). Furthermore, differences in 25OHD levels seen in mendelian randomization studies are likely to have been present since birth given the genetic influences being tested, and exposure of the vascular tree to higher levels of 25OHD during development and in subsequent decades may have small beneficial effects that cannot be replicated in shorter-term intervention studies.

Conclusion

The results of this analysis do not support the use of vitamin D or its analogues as an individual patient treatment for hypertension or as a population-level intervention to lower BP. The lack of efficacy of vitamin D treatment on blood pressure also argues against routine measurement of 25OHD levels in patients with hypertension.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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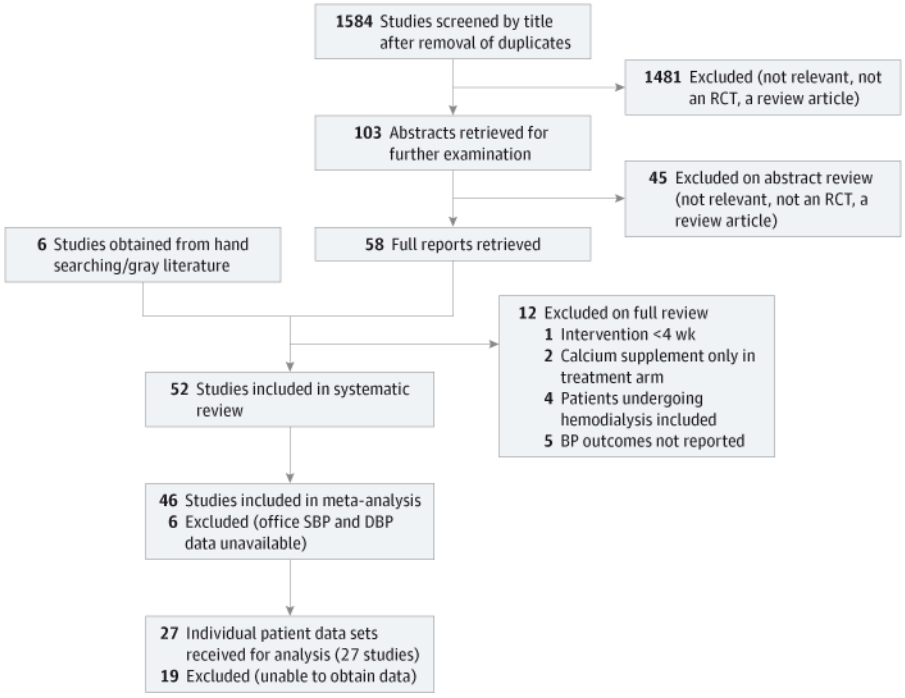


Figure 1. PRISMA Diagram of Study Selection

Gray literature indicates material not published in recognized scientific journals; BP, blood pressure; DBP, diagnostic BP; RCT, randomized clinical trial; and SBP, systolic BP.

Source	Treatment Group, No. of Patients: Vitamin D Supplement	Treatment Group, No. of Patients: Placebo	Difference in Mean SBP Between Groups (95% CI)
Lind et al,[15] 1987	15	10	−4.0 (−21.8 to 13.8)
Lind et al,[16] 1988	15	16	3.0 (−7.7 to 13.7)
Lind et al,[17] 1988	33	32	−4.0 (−13.5 to 5.6)
Lind et al,[18] 1989	18	21	5.0 (−4.9 to 14.9)
Scragg et al,[21] 1995	95	94	0.0 (−4.2 to 4.2)
Pfeifer et al,[22] 2001	73	72	−6.5 (−12.4 to −0.6)
Sugden et al,[5] 2008	17	17	−13.9 (−21.2 to 6.6)
Nagpal et al,[24] 2009	35	36	4.0 (−0.0 to 7.9)
Ziiterman et al,[25] 2009	82	83	−1.0 (−5.9 to 3.9)
de Zeeuw et al,[29] 2010	92	88	−5.0 (−16.1 to 6.1)
Jorde et al,[26] 2010	114	112	2.3 (−0.9 to 5.5)
Witham et al,[28] 2010	48	48	2.0 (−6.8 to 10.8)
Witham et al,[27] 2010	19	21	−2.3 (−14.2 to 9.6)
Harris et al,[30] 2011	22	23	1.5 (−3.6 to 6.6)
Shab-Bidar et al,[31] 2011	50	50	−4.8 (−11.3 to 1.7)
Alvarez et al,[32] 2012	17	20	8.4 (−6.6 to 23.4)
Bonakdaran et al,[33] 2012	15	16	−6.6 (−14.7 to 1.5)
Gepner et al,[34] 2012	55	55	2.2 (−1.4 to 5.8)
Heshmat et al,[35] 2012	21	21	0.0 (−0.5 to 0.5)
Kjaergaard et al,[36] 2012	120	110	0.0 (−2.8 to 2.8)
Muldowney et al,[39] 2012	51	56	2.0 (−3.6 to 7.6)
Muldowney et al,[39] 2012	48	52	−1.0 (−8.9 to 6.9)
Salehpour et al,[40] 2012	40	37	2.7 (−2.5 to 7.9)
Stricker et al,[41] 2012	31	31	0.0 (−9.2 to 9.2)
Witham et al,[42] 2012	29	27	−0.4 (−7.9 to 7.1)
Wood et al,[43] 2012	95	98	0.9 (−2.2 to 4.0)
Asemi et al,[44] 2013	24	24	−5.7 (−9.9 to 1.5)
Boxer et al,[45] 2013	24	24	−0.3 (−6.7 to 8.1)
Breslavsky et al,[46] 2013	19	13	0.4 (−10.4 to 11.2)
Chai et al,[47] 2013	22	21	3.7 (−5.5 to 12.9)
Forman et al,[48] 2013	70	72	−5.7 (−11.5 to 0.1)
Larsen et al,[49] 2013	26	26	2.0 (−4.5 to 8.5)
Petchey et al,[50] 2013	11	14	0.2 (−13.5 to 13.9)
Roth et al,[51] 2013	67	65	0.9 (−2.9 to 4.7)
Toxqui et al,[52] 2013	55	54	−4.1 (−11.7 to 3.5)
Wamberg et al,[53] 2013	22	21	−5.0 (−14.6 to 4.6)
Witham et al,[54] 2013	73	69	1.7 (−3.2 to 6.6)
Witham et al,[55] 2013	38	36	−0.9 (−7.4 to 5.6)
Witham et al,[56] 2013	24	25	2.9 (−1.9 to 7.7)
Yiu et al,[57] 2013	50	50	3.0 (−3.3 to 9.3)
Dalbeni et al,[58] 2014	13	13	−2.8 (−19.9 to 14.3)
Scragg et al,[59] 2014	149	151	−1.0 (−3.3 to 1.3)
Sollid et al,[60] 2014	242	242	0.6 (−2.0 to 3.2)
Strobel et al,[61] 2014	39	36	1.3 (−6.4 to 9.0)
Wang et al,[62] 2014	30	30	4.0 (−4.4 to 12.4)
Witham et al,[63] 2014	31	30	2.7 (−5.2 to 10.6)
Overall effect			−0.0 (−0.8 to 0.8)

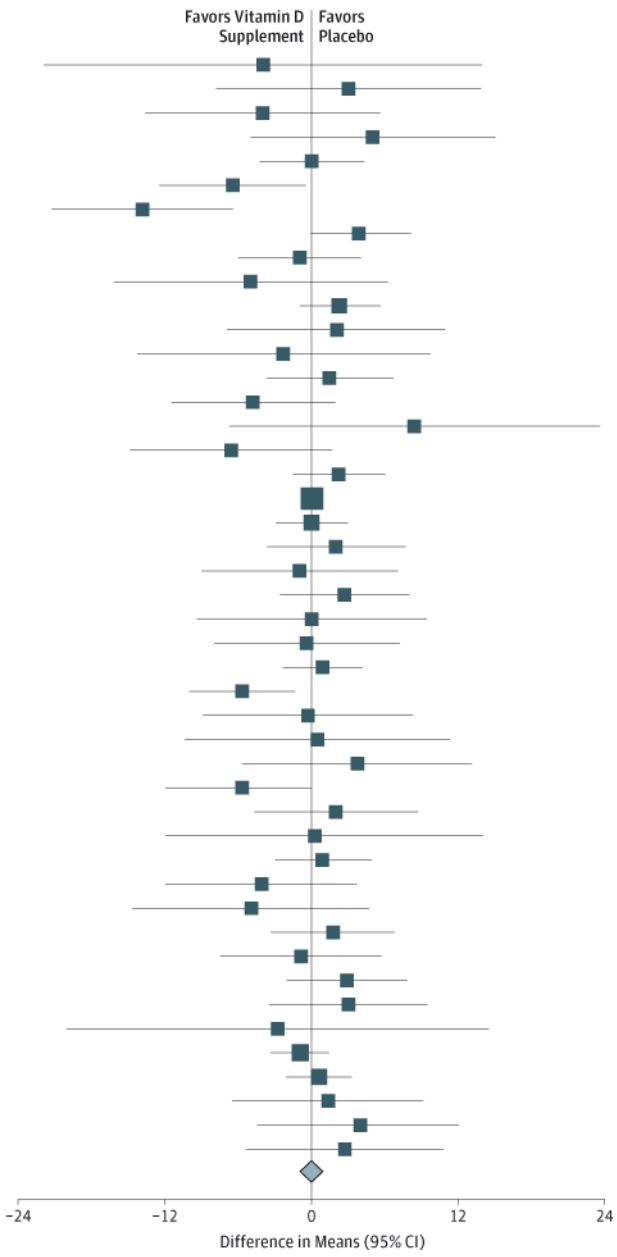
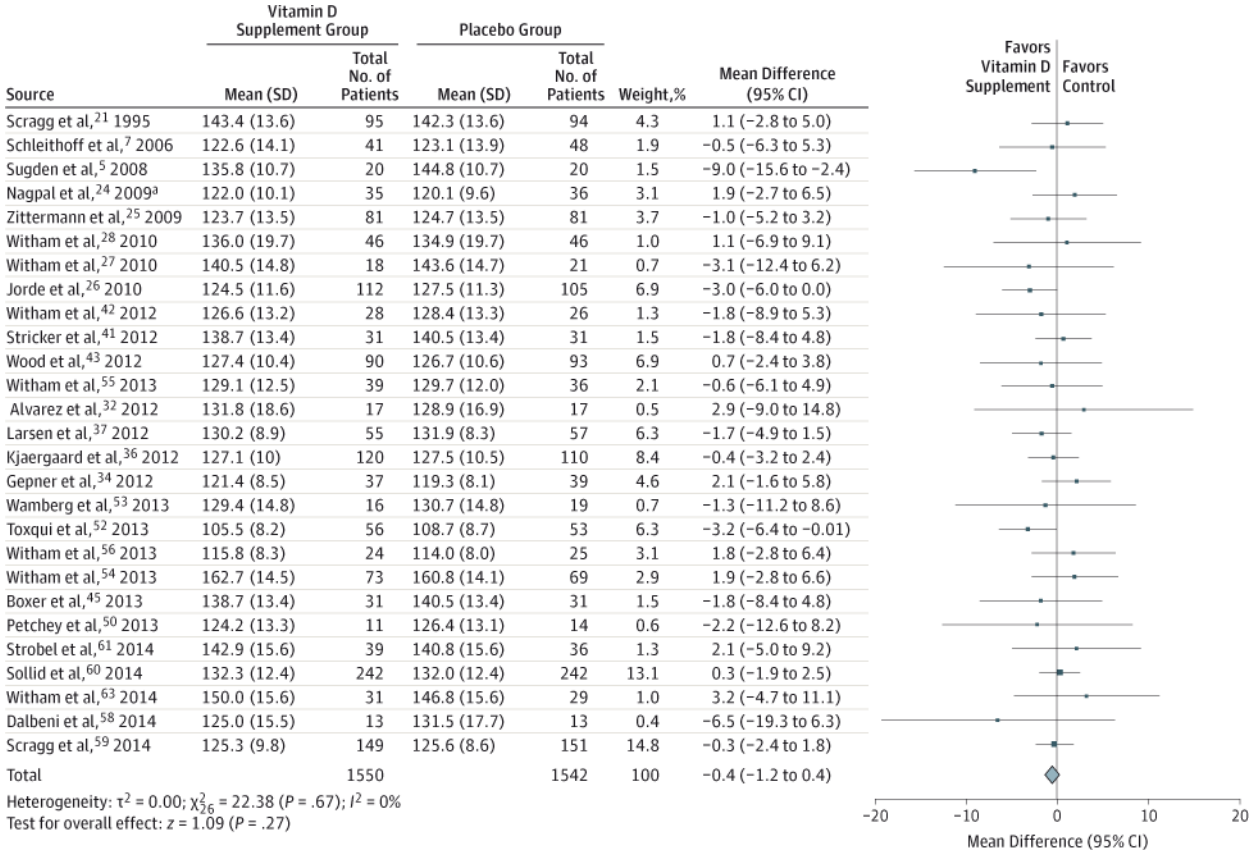


Figure 2. Results of Trial-Level Meta-analysis for Systolic Blood Pressure Outcomes

Different sizes of data markers correspond to the relative weight assigned in the pooled analysis. Diamond marker indicates the overall result.



Source	Vitamin D Supplement Group: Mean (SD)	Vitamin D Supplement Group: Total No. of Patients	Placebo Group: Mean (SD)	Placebo Group: Total No. of Patients	Weight,%	Mean Difference (95% CI)
Scragg et al,[21] 1995	143.4 (13.6)	95	142.3 (13.6)	94	4.3	1.1 (−2.8 to 5.0)
Schleithoff et al,[7] 2006	122.6 (14.1)	41	123.1 (13.9)	48	1.9	−0.5 (−6.3 to 5.3)
Sugden et al,[5] 2008	135.8 (10.7)	20	144.8 (10.7)	20	1.5	−9.0 (−15.6 to −2.4)
Nagpal et al,[24] 2009[a]	122.0 (10.1)	35	120.1 (9.6)	36	3.1	1.9 (−2.7 to 6.5)
Zittermann et al,[25] 2009	123.7 (13.5)	81	124.7 (13.5)	81	3.7	−1.0 (−5.2 to 3.2)
Witham et al,[28] 2010	136.0 (19.7)	46	134.9 (19.7)	46	1.0	1.1 (−6.9 to 9.1)
Witham et al,[27] 2010	140.5 (14.8)	18	143.6 (14.7)	21	0.7	−3.1 (−12.4 to 6.2)
Jorde et al,[26] 2010	124.5 (11.6)	112	127.5 (11.3)	105	6.9	−3.0 (−6.0 to 0.0)
Witham et al,[42] 2012	126.6 (13.2)	28	128.4 (13.3)	26	1.3	−1.8 (−8.9 to 5.3)
Stricker et al,[41] 2012	138.7 (13.4)	31	140.5 (13.4)	31	1.5	−1.8 (−8.4 to 4.8)
Wood et al,[43] 2012	127.4 (10.4)	90	126.7 (10.6)	93	6.9	0.7 (−2.4 to 3.8)
Witham et al,[55] 2013	129.1 (12.5)	39	129.7 (12.0)	36	2.1	−0.6 (−6.1 to 4.9)
Alvarez et al,[32] 2012	131.8 (18.6)	17	128.9 (16.9)	17	0.5	2.9 (−9.0 to 14.8)
Larsen et al,[37] 2012	130.2 (8.9)	55	131.9 (8.3)	57	6.3	−1.7 (−4.9 to 1.5)
Kjaergaard et al,[36] 2012	127.1 (10)	120	127.5 (10.5)	110	8.4	−0.4 (−3.2 to 2.4)
Gepner et al,[34] 2012	121.4 (8.5)	37	119.3 (8.1)	39	4.6	2.1 (−1.6 to 5.8)
Wamberg et al,[53] 2013	129.4 (14.8)	16	130.7 (14.8)	19	0.7	−1.3 (−11.2 to 8.6)
Toxqui et al,[52] 2013	105.5 (8.2)	56	108.7 (8.7)	53	6.3	−3.2 (−6.4 to −0.01)
Witham et al,[56] 2013	115.8 (8.3)	24	114.0 (8.0)	25	3.1	1.8 (−2.8 to 6.4)
Witham et al,[54] 2013	162.7 (14.5)	73	160.8 (14.1)	69	2.9	1.9 (−2.8 to 6.6)
Boxer et al,[45] 2013	138.7 (13.4)	31	140.5 (13.4)	31	1.5	−1.8 (−8.4 to 4.8)
Petchey et al,[50] 2013	124.2 (13.3)	11	126.4 (13.1)	14	0.6	−2.2 (−12.6 to 8.2)
Strobel et al,[61] 2014	142.9 (15.6)	39	140.8 (15.6)	36	1.3	2.1 (−5.0 to 9.2)
Sollid et al,[60] 2014	132.3 (12.4)	242	132.0 (12.4)	242	13.1	0.3 (−1.9 to 2.5)
Witham et al,[63] 2014	150.0 (15.6)	31	146.8 (15.6)	29	1.0	3.2 (−4.7 to 11.1)
Dalbeni et al,[58] 2014	125.0 (15.5)	13	131.5 (17.7)	13	0.4	−6.5 (−19.3 to 6.3)
Scragg et al,[59] 2014	125.3 (9.8)	149	125.6 (8.6)	151	14.8	−0.3 (−2.4 to 1.8)
Total		1550		1542	100	−0.4 (−1.2 to 0.4)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{26} = 22.38$ ($P = .67$); $I^2 = 0\%$
Test for overall effect: $z = 1.09$ ($P = .27$)

Figure 3. Results of Individual Patient Data Analysis Using Final Systolic Blood Pressure (BP) Adjusted for Baseline BP

Different sizes of data markers correspond to the relative weight assigned in the pooled analysis. Diamond marker indicates the overall result.

[a]Study was completed in the year before publication.

Table 1

Trial Level Results of Meta-analysis

Variable	No. of Trials	No. of Patients	Effect Size (95% CI), mm Hg	*P* Value	I^2, %	Between-Group *P* Value
Systolic Blood Pressure						
Overall	46	4541	0.0 (−0.8 to 0.8)	.97	21	NA
Mean baseline SBP >140 mm Hg	16	1361	−0.7 (−3.2 to 1.7)	.55	38	.54
Mean baseline SBP ≤140 mm Hg	30	3180	0.1 (−0.6 to 0.9)	.77	11	
Vitamin D_2 and D_3 supplements	38	4058	0.0 (−0.9 to 0.9)	.97	26	NA
1-α-Hydroxylated vitamin D derivatives	5	191	−1.6 (−6.3 to 7.1)	.50	4	.64
Paricalcitol	3	292	1.4 (−3.3 to 6.1)	.56	0	.57
Mean baseline 25OHD level ≤20 ng/mL	27	2555	−0.7 (−2.2 to 0.7)	.31	38	.31
Mean baseline 25OHD level >20 ng/mL	13	1723	0.1 (−0.4 to 0.6)	.75	0	
Daily dosing	16	1522	−0.7 (−2.5 to 1.0)	.41	24	NA
Weekly/fortnightly dosing	8	1303	1.3 (−0.1 to 2.6)	.07	0	.07
Monthly or less frequent dosing	14	1216	−0.2 (−1.6 to 1.2)	.76	28	.66
Diastolic Blood Pressure						
Overall	45	4434	−0.1 (−0.6 to 0.5)	.84	20	NA
Mean baseline SBP >140 mm Hg	14	1074	−0.4 (−2.1 to 1.3)	.61	55	.65
Mean baseline SBP ≤140 mm Hg	30	3180	0.0 (−0.4 to 0.3)	.85	0	
Vitamins D_2 and D_3 supplements	37	3951	0.1 (−0.3 to 0.5)	.65	4	NA
1-α-Hydroxylated vitamin D derivatives	5	191	−3.5 (−6.8 to −0.1)	.04	54	.04
Paricalcitol	2	112	−1.0 (−3.9 to 1.9)	.50	0	.46
Mean baseline 25OHD level ≤20 ng/mL	26	2375	0.2 (−0.5 to 1.0)	.54	17	.50
Mean baseline 25OHD level >20 ng/mL	12	1616	−0.1 (−0.5 to 0.4)	.69	0	
Daily dosing	16	1466	−0.5 (−1.5 to 0.4)	.26	23	NA
Weekly/fortnightly dosing	8	1303	0.6 (−0.4 to 1.5)	.23	0	.11
Monthly or less frequent dosing	14	1213	0.0 (−0.4 to 0.5)	.84	0	.35

Abbreviations: SBP, systolic blood pressure; NA, not applicable; 25OHD, 25-hydroxyvitamin D.

SI conversion factor: To convert 25OHD to nanomoles per liter, multiply by 2.496.

Table 2

Results of Individual Patient Data Meta-analysis

Variable	No. of Patients	Effect Size (95% CI), mm Hg	*P* Value	I^2,%	*P* Value[a]
Systolic Blood Pressure					
Overall	3092	−0.5 (−1.3 to 0.4)	.27	0	NA
Baseline SBP >140 mm Hg	926	0.1 (−2.5 to 2.6)	.97	33	.84
Baseline SBP ≤140 mm Hg	2148	−0.6 (−1.5 to 0.3)	.18	0	
Baseline 25OHD level <10 ng/mL	427	−0.4 (−3.0 to 2.3)	.80	14	NA
Baseline 25OHD level 10–20 ng/mL	1289	−0.7 (−2.0 to 0.6)	.31	0	.83
Baseline 25OHD level >20 ng/mL	1331	−0.2 (−1.8 to 1.3)	.77	26	.95
Diabetes mellitus	353	1.1 (−2.9 to 5.1)	.58	50	.46
No diabetes mellitus	2728	−0.4 (−1.3 to 0.4)	.35	0	
Using ACE inhibitors	475	−1.4 (−3.7 to 1.0)	.24	1	.31
Not using ACE inhibitors	1485	0.1 (−1.4 to 1.6)	.94	29	
Baseline PTH level >217 pg/mL	1318	−0.8 (−2.1 to 0.5)	.23	0	.76
Baseline PTH level ≤217 pg/mL	1364	−0.5 (−2.1 to 1.2)	.58	37	
Baseline adjusted serum calcium level >9.2 mg/dL	1267	−1.0 (−2.3 to 0.4)	.17	0	.39
Baseline adjusted serum calcium level ≤9.2 mg/dL	1340	0.2 (−2.2 to 2.6)	.86	64	
Diastolic Blood Pressure					
Overall	3075	0.2 (−0.3 to 0.7)	.38	0	NA
Baseline DBP >90 mm Hg	315	−0.2 (−3.3 to 2.9)	.90	52	.83
Baseline DBP ≤90 mm Hg	2736	0.1 (−0.4 to 0.7)	.60	0	
Baseline 25OHD level <10 ng/mL	427	−1.2 (−2.4 to 0.0)	.05	46	NA
Baseline 25OHD level 10–20 ng/mL	1289	−0.2 (−1.0 to 0.6)	.66	0	.11
Baseline 25OHD level >20 ng/mL	1328	0.2 (−0.5 to 0.9)	.50	23	.03
Diabetes mellitus	342	1.2 (−0.1 to 3.4)	.28	36	.32
No diabetes mellitus	2722	0.1 (−0.4 to 0.6)	.81	0	
Using ACE inhibitors	475	0.1 (−1.3 to 1.5)	.92	0	.64
Not using ACE inhibitors	1482	0.4 (−0.2 to 1.1)	.19	43	

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Variable	No. of Patients	Effect Size (95% CI), mm Hg	*P* Value	I^2,%	*P* Value[a]
Baseline PTH level >217 pg/mL	1324	0.0 (−0.8 to 0.8)	.99	0	.80
Baseline PTH level ≤217 pg/mL	1362	0.2 (−0.7 to 1.0)	.70	10	
Baseline adjusted serum calcium level >9.2 mg/dL	1266	0.1 (−0.7 to 0.9)	.73	0	.22
Baseline adjusted serum calcium level ≤9.2 mg/dL	1340	1.1 (−0.3 to 2.4)	.12	54	

Abbreviations: ACE, angiotensin converting enzyme; DBP, diastolic blood pressure; NA, not applicable; PTH, parathyroid hormone; SBP, systolic blood pressure; 25OHD, 25-hydroxyvitamin D.

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; PTH to picomoles per liter, divide by 9.43; and 25OHD to millimoles per liter, multiply by 2.496.

[a] *P* values for SBP are calculated for between-group interaction; for DBP, for interaction.